

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 September 2003 (12.09.2003)

PCT

(10) International Publication Number
WO 03/074053 A1

(51) International Patent Classification⁷: A61K 31/428,
31/423, 31/4709, 31/427, 31/4427, A61P 25/28, 35/00

(21) International Application Number: PCT/EP03/02085

(22) International Filing Date: 28 February 2003 (28.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02004745.2 1 March 2002 (01.03.2002) EP
60/361,062 1 March 2002 (01.03.2002) US

(71) Applicant (for all designated States except US): SCHERING AG [DE/DE]; Müllerstrasse 178, 13353 Berlin-Wedding (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LICHTNER, Rosemarie [DE/DE]; Belziger Str. 39, 10823 Berlin (DE). ROTGERI, Andrea [DE/DE]; Veitstr. 44, 13507 Berlin (DE). KLAR, Ulrich [DE/DE]; Isegrimsteig 8A, 13503

Berlin (DE). HOFFMANN, Jens [DE/DE]; Walterstr 13, 16567 Mühlenbeck (DE). BUCHMANN, Bernd [DE/DE]; Erdmannstr. 44, 16540 Hohen Neuendorf (DE). SCHWEDE, Wolfgang [DE/DE]; Klosterheider Weg 35, 13467 Berlin (DE). SKUBALLA, Werner [DE/DE]; Mattersburger Weg 12, 13465 Berlin (DE).

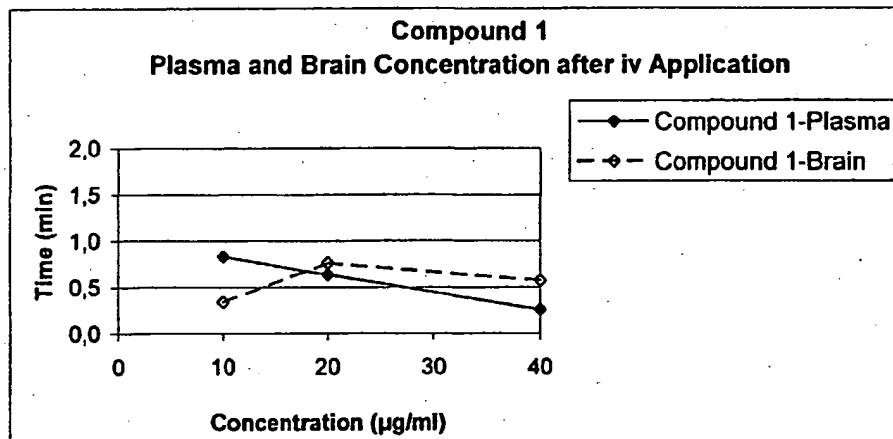
(74) Agent: DÖRRIES, FRANK-MOLNIA, POHLMAN; Triftstrasse 13, 80538 Munich (DE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: USE OF EPOTHILONES IN THE TREATMENT OF BRAIN DISEASES ASSOCIATED WITH PROLIFERATIVE PROCESSES



Compound 1: 4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-7-(1-propyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(57) Abstract: This invention provides the use of an Epothilone, which shows an average distribution coefficient between plasma and brain of 0.3 to 1.5 in the mouse intravenous bolus injection assay, for the preparation of a medicament for the treatment of a brain disease associated with proliferative processes.

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— *as to the identity of the inventor (Rule 4.17(i)) for all designations*

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Published:

— *with international search report*

**Use of Epothilones in the Treatment of Brain Diseases
Associated with Proliferative Processes**

Field of the Invention

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The present invention relates to the use of Epothilones in the treatment of brain diseases associated with proliferative processes, especially primary or secondary brain tumors, multiple sclerosis, and Alzheimer's disease.

10 **Background of the Invention**

The possibilities of medicamentous treatment of brain diseases are strongly limited by the existence of the so-called blood-brain-barrier (BBB). While the BBB serves as a protective mechanism for preventing exogenous substances to enter the brain tissue, 15 unfortunately, it also prevents the entry of drugs administered by a conventional mode (orally, parenterally, etc.) (A. Maelicke, *Nachr. Chem Tech. Lab.* 1989, 37, 32-34).

An important class of brain diseases which are difficult to treat with medicaments for the above-cited reason are diseases associated with proliferative processes such as brain 20 tumors, multiple sclerosis, or Alzheimer's disease. Various studies regarding these diseases, especially cancer, have provided some insights into the efficiency of drug targeting to the brain (W. Shapiro, J. Shapiro, *Semin. Oncol.* 1986, 13, 56-69; M. Donelli et al., *Cancer Chemother. Pharmacol.* 1992, 30, 251-260). As a rule of thumb, a drug reaches higher concentrations in the brain the lower its molecular mass and the 25 higher its lipophilicity is (C. Unger et al., *Klin. Wochenschr.* 1985, 63, 565-571). Nevertheless, it has been found in recent years, that for at least some compounds (M. Fromm, *Int. J. Clin. Pharmacol. Ther.* 2000, 38, 69-74) active exclusion mechanisms exist within the BBB, so that drug uptake by brain tissue cannot be simply calculated from physical or chemical data but has to be determined experimentally.

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- Some experimental methods have been developed to overcome the restrictions of drug uptake by brain tissue caused by the BBB; e.g., direct intrathecal drug application, use of lipid-soluble carriers, or disruption of the BBB by application of high doses of mannitol or other compounds (E. Galanis et al., *Curr. Opin. Neurol.* 2000, 13, 619-625; 5 H. Lahrman et al., *J. Neurol. Neurochir. Psychiatr.* 2001, 2, 16-20). These methods are, however, associated with considerable disadvantages and/or undesirable side effects. Most of them can be considered to be in an experimental stage, i.e., they cannot be considered as standard therapies.
- 10 As a result of the previous work it can be stated that most cytostatic agents (which is the most important class of drugs for the treatment of diseases associated with proliferative processes) do not reach the same concentration in brain liquor as in blood plasma when applied systemically. For example, it has lately been found that maximum liquor concentrations of 20-30% of the plasma concentrations may be reached when using 15 nitrosoureas, which are considered to be the best BBB penetrating type of cytostatic agents (*Therapiekonzepte Onkologie*; Seeberger, S, Schütte, J. (Eds.), 3rd edition, Springer, Berlin 1998). Nitrosoureas and a combination of nitrosoureas with procarbazine and vincristine (PCV therapy) are considered to be standard chemotherapeutic agents for the treatment of brain cancer (H. Lahrman et al., *J.* 20 *Neurol. Neurochir. Psychiatr.* 2001, 2, 16-20; E. Galanis et al., *Curr. Opin. Neurol.* 2000, 13, 619-625).

- Cytostatic agents can be distinguished according to the mechanism of their pharmacological activity. The most important classes of cytostatic compounds are 25 antimetabolites (e.g. fluorouracil, cytarabine, mercaptopurine), antimitotic agents (e.g. colchicine, paclitaxel, podophyllotoxine, *Vinca*-alkaloids), alkylating agents (e.g. cisplatin, nitrosoureas, nitrogen mustards), antibiotics (e.g. bleomycin), and agents in respect of which the mechanism of their therapeutic effectiveness is not known (e.g. asparaginase).

Although alkylating agents have been found to be useful for cancer treatment, it is an enormous disadvantage of these compounds that their pharmacological mechanism bears a strong carcinogenic potential itself.

- 5 In particular nitroso compounds (nitrosoureas and nitroso amines), which were discussed above to be efficient drugs for the treatment of the brain, show these effects: 57 of 60 nitrosoureas (95 %) tested on carcinogenic activity were active (CD Römpp Chemie Lexikon – Version 1.0, Stuttgart/New York: Georg Thieme Verlag 1995). It would thus be desirable to provide compounds for the efficient treatment of brain
10 diseases associated with proliferative processes which have similar or better BBB-penetrating properties as nitrosoureas, but without their carcinogenic potential.

- Within the group of antimitotic agents, Paclitaxel (Taxol®) is the best-known member and one of the best-selling anticancer medicaments in the present time. Unfortunately,
15 paclitaxel has only low ability to penetrate the BBB (M. Glantz et al., *J. Natl. Cancer Inst.* 1995, 87, 1077-1081) and is thus not considered to be useful for the treatment of brain diseases via conventional administration routes. Other antimitotic agents, which block the mitotic spindle of a proliferating cell by binding to the spindle-peptide tubulin, and thus cause apoptosis, have been found to be powerful anticancer agents
20 (K.-H. Altmann, *Curr. Opin. Chem. Biol.* 2001, 5, 424-431), in respect of which less carcinogenic side effects have been reported than in the case of the alkylating agents discussed above. Epothilones also belong to this group of drugs.

- The natural products Epothilone A and B as well as some of their synthetic derivatives
25 have recently found interest in connection with the treatment of cancer, and a lot of work has been done on their synthesis (K. Nicolaou et al., *Angew. Chem.* 1998, 110, 2120-2153) and the synthesis of modified structures.

- WO 99/07692, WO 99/02514 and WO 99/67252 disclose Epothilone derivatives, their
30 synthesis and pharmaceutical use.

WO 00/66589 deals with the synthesis and pharmaceutical use of Epothilone derivatives having an alkenyl-, alkynyl-, or an cyclic ether containing substituent at the 6-position of the macrocyclic ring.

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WO 00/49021 discloses Epothilone derivatives with a halogen substituent in 16-position and their synthesis.

WO 00/71521 discloses a method for the synthesis of olefinic Epothilones.

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WO 98/25929 deals with the manufacture of libraries of Epothilone analogs.

WO 99/43320 mentions, in a very general manner, the use of Epothilones for the treatment of cancer. The disclosure focuses on the development of application conditions for the particular compound Epothilone B for the treatment of a wide range of cancer varieties. There is no mention in this document of the difficulties of treating brain diseases associated with proliferative processes as discussed above, or of any specific advantages of using Epothilones in this regard.

20 It has now unexpectedly been found that certain Epothilones show a particularly good ability to penetrate the BBB compared to other cytostatic agents (antimitotic agents and others), and thus, are particularly useful for the manufacture of medicaments for the treatment of brain diseases associated with proliferative processes. Due to their pharmacological mechanism of action, these compounds can also be used for the treatment of diseases other than cancer, which are associated with proliferative activity.

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Summary of the Invention

Accordingly, the present invention relates to the use of Epothilones for the treatment of brain diseases associated with proliferative processes, or for the preparation of a

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medicament for the treatment of brain diseases associated with proliferative processes. It also relates to methods of treating brain diseases associated with proliferative processes by oral, rectal, local, or parenteral, preferably inhalational, intravenous, or intraperitoneal, most preferably intravenous administration of an Epothilone.

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For the purposes of the present invention, an Epothilone is defined as a cyclic molecule with a 16-membered ring and variable substituents and pharmaceutical activity as a cytostatic agent that binds to tubulin (Asnes et al., *Anal. Biochem.* 1979, 98, 64-73; Job et al., *Cellular Pharmacol.* 1993, I (Suppl. I), S7-S10; Lichtner et al., *PNAS* 2001, 98, 11743-11748). The preferred Epothilones for use according to the present invention furthermore show an average distribution coefficient between plasma and brain of 0.3 to 1.5 as measured by the mouse bolus injection assay, as described herein.

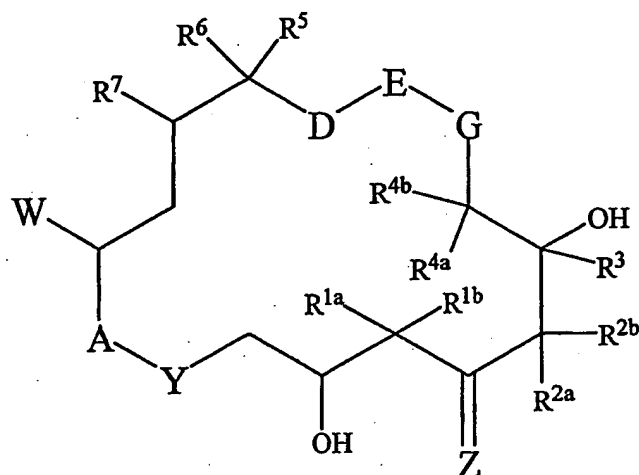
A further preferred subgroup is that wherein the Epothilone molecule is a lactone or a lactame molecule.

15 A preferred subgroup is that wherein the Epothilone shows an average distribution coefficient between plasma and brain of 0.6 to 1.2 in the mouse intravenous bolus injection assay.

A preferred subgroup is the use for the treatment of a brain disease selected from the group consisting of primary brain tumor, secondary brain tumor, Alzheimer's disease and multiple sclerosis.

20

Preferred Epothilones for use in the present invention are compounds of the general formula:



wherein:


5 R^{1a}, R^{1b} are each independently hydrogen, C₁-C₁₀ alkyl, aryl, aralkyl, or together form a -(CH₂)_m-group where m is 2 to 5;

10 R^{2a}, R^{2b} are each independently hydrogen, C₁-C₁₀ alkyl, aryl, aralkyl, or together form a -(CH₂)_n-group where n is 2 to 5, or C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl;

15 R³ is hydrogen, C₁-C₁₀ alkyl, aryl, aralkyl;

20 R^{4a}, R^{4b} are each independently hydrogen, C₁-C₁₀ alkyl, aryl, aralkyl, or together form a -(CH₂)_p- group where p is 2 to 5;

25 R⁵ is hydrogen, C₁-C₁₀ alkyl, aryl, aralkyl, CO₂H, CO₂alkyl, CH₂OH, CH₂Oalkyl, CH₂Oacyl, CN, CH₂NH₂, CH₂N(alkyl, acyl)_{1,2}, or CH₂Hal;

- R^6, R^7 are each hydrogen, or together form an additional bond, or together form an epoxy function;
- G is O or CH_2 ;
- $D-E$ is a group H_2C-CH_2 , $HC=CH$, $C\equiv C$, $CH(OH)-CH(OH)$, $CH(OH)-CH_2$,
 $CH_2-CH(OH)$, CH_2-O , $O-CH_2$; ;
- W is a group $C(=X)R^8$, or is a bi- or tricyclic aromatic or heteroaromatic radical;
- X is O, or two groups OR^{20} , or a C_2-C_{10} alkylenedioxy group (which may be straight or branched), or H/OR^9 , or a group $CR^{10}R^{11}$;
- R^8 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, halogen, CN;
- R^9 is hydrogen or a protecting group PG^X ;
- R^{10}, R^{11} are each independently hydrogen, C_1-C_{20} alkyl, aryl, aralkyl, or together with the methylene carbon form a 5- to 7-membered carbocyclic ring;
- Z is O or H/OR^{12} ;
- R^{12} is hydrogen or a protecting group PG^Z ;

A-Y is a group O-C(=O), O-CH₂, CH₂-C(=O), NR²¹-C(=O), NR²¹-SO₂;

R²⁰ is a C₁-C₂₀ alkyl group;

R²¹ is hydrogen, or C₁-C₁₀ alkyl;

PG^x, PG^z is C₁-C₂₀ alkyl, C₄-C₇ cycloalkyl, which may contain an oxygen atom in the ring, aryl, aralkyl, C₁-C₂₀ acyl, aroyl, C₁-C₂₀ alkylsulfonyl, arylsulfonyl, tri(C₁-C₂₀ alkyl)silyl, di(C₁-C₂₀ alkyl) arylsilyl, (C₁-C₂₀ alkyl)diarylsilyl, or tri(aralkyl)silyl;

as a single stereoisomer or a mixture of different stereoisomers,
and / or as a pharmaceutically acceptable salt thereof.

These compounds are advantageously used in the treatment of, or for the manufacture of a medicament for the treatment of, a brain disease associated with proliferative processes.

In a further embodiment, the present invention relates to a method of treating a brain disease associated with proliferative processes comprising administering to an individual in need thereof a therapeutically effective amount of an Epothilone as defined above.

Preferred Embodiments

The term "brain disease associated with proliferative processes" as referred to in the context of the present invention includes, but is not limited to, primary brain tumors such as astrocytomas, oligodendrogliomas, pinealomas, medulloblastomas, neurilemmomas, meningiomas, and ependymomas, secondary brain tumors, multiple

sclerosis, and Alzheimer's disease, all of which represent preferred brain diseases associated with proliferative processes to be treated in accordance with the present invention.

- 5 Particularly preferred brain diseases associated with proliferative processes to be treated by Epothilone administration in accordance with the present invention are primary and secondary brain tumors.

10 The term "therapeutically effective amount" as used herein refers to that amount of a compound of the invention which, when administered to an individual in need thereof, is sufficient to effect treatment, as defined below, for brain diseases associated with proliferative processes. The amount which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease and its severity, and the age of the human to be treated, but can be determined routinely by one of ordinary skill in
15 the art having regard to his own knowledge and to this disclosure.

"Treating" or "treatment" as used herein refers to the treatment of a brain disease in an individual, which disease is associated with proliferative processes; and include:

- 20 (i) preventing the disease from recurring in an individual, in particular, when such individual is in need of further medicamentous treatment after a previous surgical or medicamentous therapy;
- (ii) inhibiting the disease, i.e., arresting its development; or
- (iii) relieving the disease, i.e., causing regression of the disease.

25 The term "alkyl" as used herein refers to straight or branched alkyl groups, e. g., methyl, ethyl, propyl, isopropyl, *n*-butyl, *t*-butyl, *n*-pentyl, neopentyl, heptyl, or decyl. Alkyl groups can be perfluorated or substituted by one to five substituents selected from the group consisting of halogen, hydroxy, C₁-C₄ alkoxy, or C₆-C₁₂ aryl (which can be substituted by one to three halogen atoms).

The term "aryl" as used herein refers to an aromatic carbocyclic or heterocyclic moiety containing five to 14 ring atoms, e.g., phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, chinolyl, or thiazolyl. Aryl groups can be substituted by one or more substituents selected from the group consisting of halogen, hydroxy, alkoxy, -CO₂H, -CO₂Alkyl, -NH₂, -NO₂, -N₃, -CN, C₁-C₂₀ alkyl, C₁-C₂₀ acyl, or C₁-C₂₀ acyloxy. The heteroatoms can be oxidized, if this does not cause a loss of aromatic character, e. g., a pyridine moiety can be oxidized to give a pyridine N-oxide.

10 The term "aralkyl" as used herein refers to a group which can contain up to 14 atoms in the aryl ring (preferred five to ten) and one to eight carbon atoms in the alkyl chain (preferred one to four), e.g., benzyl, phenylethyl, naphthylmethyl, naphthylethyl, furylmethyl, thienylethyl, or pyridylpropyl. The rings can be substituted by one or more substituents selected from the group consisting of halogen, hydroxy, alkoxy, -CO₂H, -CO₂Alkyl, -NH₂, -NO₂, -N₃, -CN, C₁-C₂₀ alkyl, C₁-C₂₀ acyl, or C₁-C₂₀ acyloxy.

The protecting groups PG can be alkyl- and/or aryl-substituted silyl moieties, C₁-C₂₀ alkyl, C₄-C₇ cycloalkyl, which may contain an oxygen atom in the ring, aryl, aralkyl, C₁-C₂₀ acyl, aroyl, alkyl- or arylsulfonyl. Groups which can be easily be removed from the molecule are preferred, e.g., methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, as well as alkylsulfonyl or arylsulfonyl. Preferred acyl groups are formyl, acetyl, propionyl, pivaloyl, butyryl, or benzoyl, which all can be substituted by one or more amino and/or hydroxy moieties.

A preferred group is compounds of the general formula as given above, wherein A-Y is O-C(=O); D-E is H₂C-CH₂; G is CH₂; Z is O; R^{1a}, R^{1b} are both C₁-C₁₀ alkyl or form together a -(CH₂)_p- group where p is 2 to 3; R^{2a}, R^{2b} are each independently hydrogen,

C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl; R³ is hydrogen; R^{4a}, R^{4b} are each independently hydrogen or C₁-C₁₀ alkyl; R⁵ is C₁-C₁₀ alkyl.

Another preferred group is compounds of the general formula as given above, wherein
 5 R^{2a}, R^{2b} are each independently hydrogen, C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl; R⁶, R⁷ form an epoxy function or together form an additional bond; W is a 2-Methylbenzothiazol-5-yl radical or a 2-Methylbenzoxazol-5-yl radical or a Quinoline-7-yl radical.

10 Of this group, a preferred subgroup is compounds selected from the following:

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzoxazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-
 15 2-(2-methyl-benzoxazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

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(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-9,13-dimethyl-5,5-(1,3-trimethylen)-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-12,16-dimethyl-8,8-(1,3-trimethylen)-4,17-
 30 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-in-1-yl)-cyclohexadec-13-ene-2,6-dione;

- 5 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-in-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

- 10 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(chinolin-2-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(chinolin-2-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-aza-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione; and

- 20 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione.

- 25 Another preferred group of compounds has the general formula as given above, wherein R^{2a} , R^{2b} are each independently hydrogen, or C_1 - C_{10} alkyl; R^6 , R^7 form an epoxy function, or form an additional bond; W is a group $C(=X)R^8$; X is a group $CR^{10}R^{11}$; R^8 is hydrogen, halogen, C_1 - C_{10} alkyl; R^{10} , R^{11} are hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl.

Of this group, a preferred subgroup is compounds selected from the following:

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

5 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;

20 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione;

25

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

5 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

20 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-12,16-dimethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

- (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;
- 5 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;
- (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-propyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;
- (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-
- 20 dione;
- (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;
- 25 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylen)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylen)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;

10

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione;

20

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-10,12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;
and

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

5

Another preferred group is compounds of the general formula as given above, wherein R^{2a} , R^{2b} are each independently hydrogen, C_2 - C_{10} alkenyl or C_2 - C_{10} alkynyl; R^6 , R^7 form an epoxy function or together form an additional bond; W is a group $C(=X)R^8$; X is a group $CR^{10}R^{11}$; R^8 is hydrogen, halogen, C_1 - C_{10} alkyl; R^{10} , R^{11} are hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl.

10

Of this group, a preferred subgroup is compounds selected from the following:

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-in-1-yl)-cyclohexadec-13-ene-2,6-dione;

15

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-in-1-yl)-3-(2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(but-3-in-1-yl)-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-en-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

- 5 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-en-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

- 10 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-en-1-yl)-3-(2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

- 15 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

- (1S/R,3S(Z),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione; and

- 25 (1S/R,3S(Z),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

The synthesis of the compounds listed above is described in the international patent applications WO 99/07692, WO 00/49021, and WO 00/66589, which are incorporated herein by reference.

- 5 For the use according to the invention, the compounds can be formulated by methods known in the art. Compositions for the oral, rectal, parenteral or local application can be prepared in the form of tablets, capsules, granulates, suppositories, implantates, sterile injectable aqueous or oily solutions, suspensions or emulsions, aerosols, salves, creams, or gels, retard preparations or retard implantates. The compounds may also be
10 administered by implantable dosing systems.

- The pharmaceutical active compound(s) can thus be mixed with adjuvants known in the art, such as gum arabic, talcum, starch, mannitol, methyl cellulose, lactose, surfactants such as tweens® or myrj®, magnesium stearate, aqueous or non-aqueous carriers,
15 paraffin derivatives, wetting agents, dispersing agents, emulsifiers, preservatives, and flavors.

- The compounds can be used in the form of their clathrates of α -, β -, or γ -cyclodextrin or of substituted α -, β -, or γ -cyclodextrines, or in the form of a liposomal composition, in
20 particular a liposomal composition comprising a polyethyleneglycol(PEG)-derivatized lipid.

- The invention also relates to pharmaceutical compositions containing one or more of the pharmaceutically active compounds listed above, and their use for the treatment and in
25 the methods in accordance with the present invention. Preferably, one dose unit of these compositions contains about 0.01-100 mg of the pharmaceutically active compound(s). The dosage for the use according to the invention for a human is about 0.01-100 mg per day; a preferred dosage is about 0.02-70 mg per day; a more preferred dosage is about 0.04-40 mg per day.

Brief Description of the Figures

Figure 1 shows the plasma and brain concentrations of 4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-7-(1-propyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione (compound 1) after iv application, monitored over a period of 40 min, determined in the animal model of Example 1.

Figure 2 shows the plasma and brain concentrations of ³H-labeled dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (compound 2) after iv application, monitored over a period of 40 min, determined in the animal model of Example 1.

Figure 3 shows the plasma and brain concentrations of ³H-labeled 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (compound 3) after iv application, monitored over a period of 40 min, determined in the animal model of Example 1.

Figure 4 shows the plasma and brain concentrations of ³H-labeled paclitaxel after iv application, monitored over a period of 40 min, determined in the animal model of Example 1.

Figure 5 shows the brain-plasma-ratio after iv application of the Epothilones of figures 1-3 and paclitaxel as comparison, monitored over a period of 40 minutes, derived from the data of figures 1-4.

Figure 6 shows the evaluation of s.c. tumor growth inhibition by treatment with 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione based on tumor volume during the

study of Example 2. The changes of the tumor volume in correlation with the time is shown for the control group A (♦) and the treatment groups B (■) and C (▲).

Figure 7 shows the evaluation of the animal body weight by treatment with 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione during the study of Example 2. The changes of the body weight in correlation with the time is shown for the control group A (♦) and the treatment groups B (■) and C (▲).

10 Example 1 (Mouse bolus injection assay)

(*In vivo* assay for the evaluation of blood and brain levels of Epothilones)

Male SCID mice (20-25 g, non-leaky) were treated with a single dose of tritium-labeled Epothilones and paclitaxel (5 mg/kg; 7.4 MBq/mg; in 30 % Hydroxypropyl-β-cyclodextrin (HPβCD)/NaCl iv bolus injection). Partitioning of radioactivity between blood and brain was measured by liquid scintillation counting (LSC) and HPLC-radioflow at three time points (10, 20 and 40 min) after injection.

The following compounds were tested in this assay:

20 Paclitaxel;

compound 1: 4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-7-(1-propyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione;

compound 2: dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; and

25 compound 3: 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

Results:

All Epothilones were found in the brain at 40 min after iv application in concentrations that exceeded the plasma concentration. For compound 1 and 2 a higher brain plasma ratio was already observed after 20 min. For compound 3 at 10 and 20 minutes a high variation between the animals within one group was observed. 40 minutes after
5 application paclitaxel was detected in the brain in considerable amounts, too.

When comparing the partial (0-40 min) areas under the plasma/brain level time curve, a ratio $AUC_{\text{brain}}/AUC_{\text{plasma}}$ of approx. 1 was found (compound 1: 1.0; compound 2: 1.2; compound 3: 0.8) indicating a free access to the brain.

10

Paclitaxel was below the limit of quantitation in all brain samples but in comparable concentrations in plasma leading to a $AUC_{\text{brain}}/AUC_{\text{plasma}}$ ratio of zero.

Concentrations measured for these compounds and AUC ratios calculated thereof are
15 summarized in table 1.

Conclusion:

In contrast to paclitaxel, Epothilones seem to penetrate the blood-brain-barrier to a
20 significant extend. Persistence in the brain is longer compared to plasma.

Table 1:

Compound (³ H-labeled)	Time (min)	Plasma conc. mean, (µg/ml)	Plasma (µg*min/ml) AUC (0-40min)	Brain conc. mean, (µg/g)	Brain (µg*min/ml) AUC (0-40min)	AUC Ratio Brain/Plasma
Compound 1	10	0,8	20	0,3	21	1,0
	20	0,6		0,8		
	40	0,3		0,6		
Compound 2	10	1,6	31	1,1	35	1,2
	20	0,7		1,1		
	40	0,3		0,8		
Compound 3	10	1,2	25	0,9	20	0,8
	20	0,7		0,3		
	40	0,3		0,6		
Pacitaxel	10	0,8	19	<LOQ	0	0,0
	20	0,6		<LOQ		
	40	0,2		<LOQ		

LOQ: Limit of Quantitation

Example 2 (In vivo activity)

In vivo assay for the evaluation of efficacy of Epothilones against xenografted and intracerebral human glioma.

Female NMRI nu/nu-mice (20-28 g) were used for this experiment. Human U373 glioma cells were implanted s.c. (1×10^7 /mouse) as well as i.cer. (2×10^5 /mouse) on day 0. Treatment was started on day 7 when the s.c. tumors were approximately $0,05 \text{ cm}^3$ in size. Treatment was continued until tumor growth in the untreated control group had reached approximately $0,6 \text{ cm}^3$ in size on day 32. After termination of the experiment, the size of the brain tumors was determined (Table 2).

The following compounds were tested in this assay:

compound 3: 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

Results:

A significant therapeutic effect on s.c. (Figure 6) as well as on i.cer. U373 brain tumors is observed for compound 3 for both schedules used in comparison to the rapid growth in the untreated control (Table 2; group B vs. A and group C vs. A).

Only a moderate body weight loss (not significant) is observed in treatment groups B and C (Figure 7).

In treatment group B, 8 from 9 mice show complete remissions of the i. cer. brain tumors.

Conclusion:

From this study it can be concluded that epothilones e.g. compound 3 demonstrated remarkable antitumor efficacy in the U373 brain tumor model.

The response of the s.c. as well as i.cer. U373 model to the treatment with compound 3 is significant in comparison to the untreated control group.

Thus, epothilones, e.g. compound 3, offer the unique potential to be effective for the treatment of brain tumors also in humans.

Table 2

Group	Mice	Substance; Dose i.v. [mg/kg]/appl	Schedule (days)	Deaths / total (d)	BWC d 7-17 [%]	RTV s.c. Tumor s d 25	i. cer. Brain Tumor Volume d 32 [mm ³]
A	10	Solvent	7, 9, 11, 14, 16, 18	0/10	4	4.05	43.4
B	10	Compound 3; 9	7, 14	0/10	-7	1.15	0.002*
C	10	Compound 3; 2	7, 9, 11, 14, 16, 18	1/10 (21)	-3	1.40	0.96

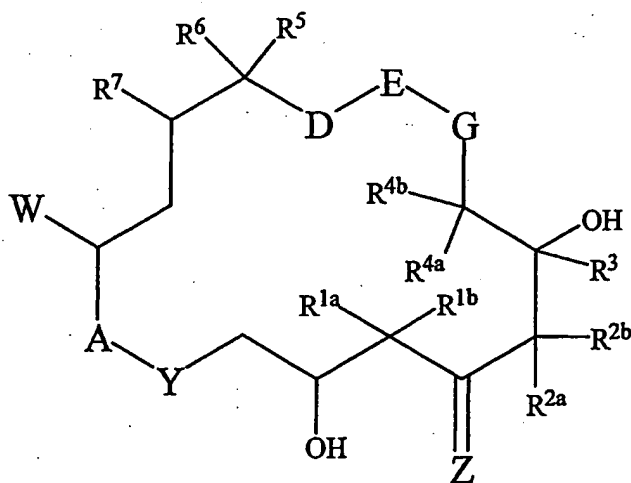
BWC: Body Weight Change; RTV: Relative Tumor Volume

*: Evaluation of one animal not possible due to incorrect implantation of i.cer. tumor.

Claims

What is claimed is:

- 5 1. Use of an Epothilone, which shows an average distribution coefficient between
 plasma and brain of 0.3 to 1.5 in the mouse intravenous bolus injection assay,
 for the preparation of a medicament for the treatment of a brain disease
 associated with proliferative processes.
- 10 2. The use of claim 1, wherein the Epothilone is a lactone or a lactame molecule.
3. The use of claim 2, wherein the average distribution coefficient between plasma
15 and brain is 0.6 to 1.2.
4. Use of a compound of the general formula:



wherein

5 R^{1a}, R^{1b} are each independently hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl, or together form a $-(CH_2)_m$ -group where m is 2 to 5;

10 R^{2a}, R^{2b} are each independently hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl, or together form a $-(CH_2)_n$ -group where n is 2 to 5, or C_2 - C_{10} alkenyl, or C_2 - C_{10} alkynyl;

R^3 is hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl;

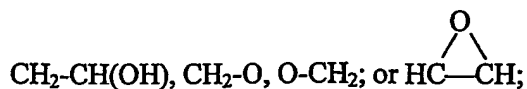
15 R^{4a}, R^{4b} are each independently hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl, or together form a $-(CH_2)_p$ - group where p is 2 to 5;

R^5 is hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl, CO_2H , CO_2 alkyl, CH_2OH , CH_2O alkyl, CH_2O acyl, CN, CH_2NH_2 , CH_2N (alkyl, acyl)_{1,2}, or CH_2Hal ;

20 R^6, R^7 are each hydrogen, or together form an additional bond, or together form an epoxy function;

G is O or CH_2 ;

25 D-E is a group H_2C-CH_2 , $HC=CH$, $C\equiv C$, $CH(OH)-CH(OH)$, $CH(OH)-CH_2$,



- W is a group $C(=X)R^8$, or is a bi- or tricyclic aromatic or heteroaromatic radical;
- 5 X is O, or two groups OR^{20} , or a C_2-C_{10} alkylenedioxy group (which may be straight or branched), or H/OR^9 , or a group $CR^{10}R^{11}$;
- R^8 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, halogen, CN;
- 10 R^9 is hydrogen or a protecting group PG^X ;
- R^{10}, R^{11} are each independently hydrogen, C_1-C_{20} alkyl, aryl, aralkyl, or together with the methylene carbon form a 5- to 7-membered carbocyclic ring;
- 15 Z is O or H/OR^{12} ;
- R^{12} is hydrogen or a protecting group PG^Z ;
- 20 A-Y is a group $O-C(=O)$, $O-CH_2$, $CH_2-C(=O)$, $NR^{21}-C(=O)$, or $NR^{21}-SO_2$;
- R^{20} is a C_1-C_{20} alkyl group;
- 25 R^{21} is hydrogen, or C_1-C_{10} alkyl;
- PG^X, PG^Z is C_1-C_{20} alkyl, C_4-C_7 cycloalkyl, which may contain an oxygen atom in the ring, aryl, aralkyl, C_1-C_{20} acyl, aroyl, C_1-C_{20} alkylsulfonyl, arylsulfonyl, $tri(C_1-C_{20} \text{ alkyl})\text{silyl}$, $di(C_1-C_{20} \text{ alkyl})\text{arylsilyl}$, $(C_1-C_{20} \text{ alkyl})\text{diarylsilyl}$, or $tri(\text{aralkyl})\text{silyl}$;
- 30

as a single stereoisomer or a mixture of different stereoisomers,
and / or as a pharmaceutically acceptable salt thereof,

5 for the preparation of a medicament for the treatment of a brain disease
associated with proliferative processes.

10 5. The use of any one of claims 1-4, where the brain disease is selected from the
group consisting of primary brain tumor, secondary brain tumor, Alzheimer's
disease and multiple sclerosis.

15 6. The use of any one of claims 4 or 5, wherein

A-Y is O-C(=O);

D-E is H₂C-CH₂;

20

G is CH₂;

Z is O;

25

R^{1a}, R^{1b} are both C₁-C₁₀ alkyl or together form a -(CH₂)_m- group where m
is 2 or 3;

R^{2a}, R^{2b} are each independently hydrogen, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or
C₂-C₁₀ alkynyl;

30

R³ is hydrogen;

R^{4a}, R^{4b} are each independently hydrogen or C₁-C₁₀ alkyl;

5 R⁵ is C₁-C₁₀ alkyl.

7. The use of any one of claims 4-6, wherein

10 R^{2a}, R^{2b} are each independently hydrogen, C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl;

R⁶, R⁷ together form an epoxy function or an additional bond; and

15 W is a 2-Methylbenzothiazol-5-yl radical, a 2-Methylbenzoxazol-5-yl radical, or a Quinoline-7-yl radical.

8. The use of claim 7, wherein the compound is selected from the group consisting
20 of:

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzoxazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

25 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzoxazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-9,13-dimethyl-5,5-(1,3-trimethylen)-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

10

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-12,16-dimethyl-8,8-(1,3-trimethylen)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-in-1-yl)-cyclohexadec-13-ene-2,6-dione;

20

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-in-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(chinolin-2-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

30

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(chinolin-2-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-aza-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

30

and

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione.

5

9. The use of any one of claims 4-6, wherein

R^{2a}, R^{2b} are each independently hydrogen, or C_1 - C_{10} alkyl;

10 R^6, R^7 together form an epoxy function or an additional bond;

W is a group $C(=X)R^8$;

X is a group $CR^{10}R^{11}$;

15

R^8 is hydrogen, halogen, or C_1 - C_{10} alkyl; and

R^{10}, R^{11} are hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl.

20

10. The use of claim 9, wherein the compound is selected from the group consisting of:

25 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

- (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;
- 5
- (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10
- (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;
- 15
- (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20
- (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione;
- 25
- (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione;

10 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

20 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-12,16-dimethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione;

25 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

5 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;

15 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-propyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;

20 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

30 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylen)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

- (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione;
- 5 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylen)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;
- (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione;
- 20 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-10,12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;
- 25 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione; and

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

11. The use of any one of claims 4-6, wherein

R^{2a}, R^{2b} are each independently hydrogen, C_2 - C_{10} alkenyl or C_2 - C_{10} alkynyl;

R^6, R^7 together form an epoxy function or an additional bond;

W is a group $C(=X)R^8$;

X is a group $CR^{10}R^{11}$;

R^8 is hydrogen, halogen, or C_1 - C_{10} alkyl; and

R^{10}, R^{11} are hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl.

12. The use of claim 11, wherein the compound is selected from the group consisting of:

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-in-1-yl)-cyclohexadec-13-ene-2,6-dione;

- (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-in-1-yl)-3-(2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 5
- (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;
- (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10
- (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(but-3-in-1-yl)-cyclohexadec-13-ene-2,6-dione;
- 15
- (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-in-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-en-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20
- (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-en-1-yl)-3-(2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 25
- (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-in-1-yl)-cyclohexadec-13-ene-2,6-dione;
- 30

(1S/R,3S(Z),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-in-1-yl)-3-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione; and

10

(1S/R,3S(Z),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

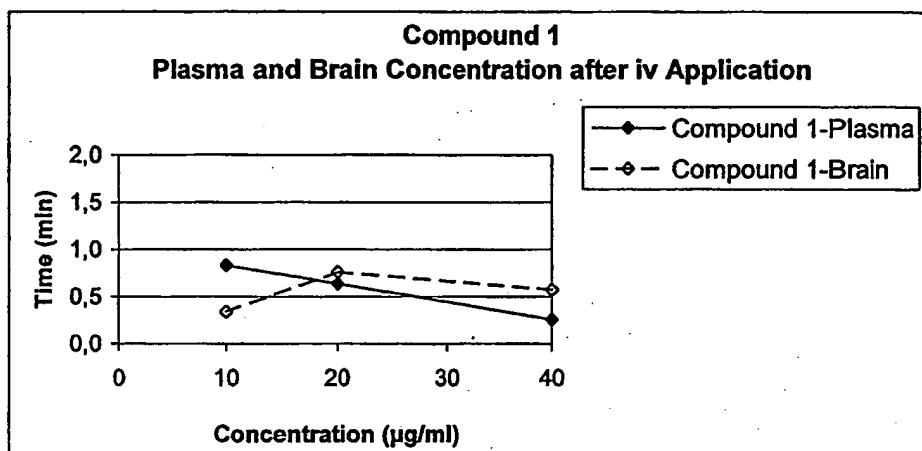
15

13. A method of treating a brain disease associated with proliferative processes comprising administering to an individual in need thereof a therapeutically effective amount of an Epothilone as defined in any one of claims 1 to 12.

20

14. The use or the method according to any one of claims 1 to 12, wherein the medicament or the Epothilone is to be administered orally, parenterally, rectally, or locally.

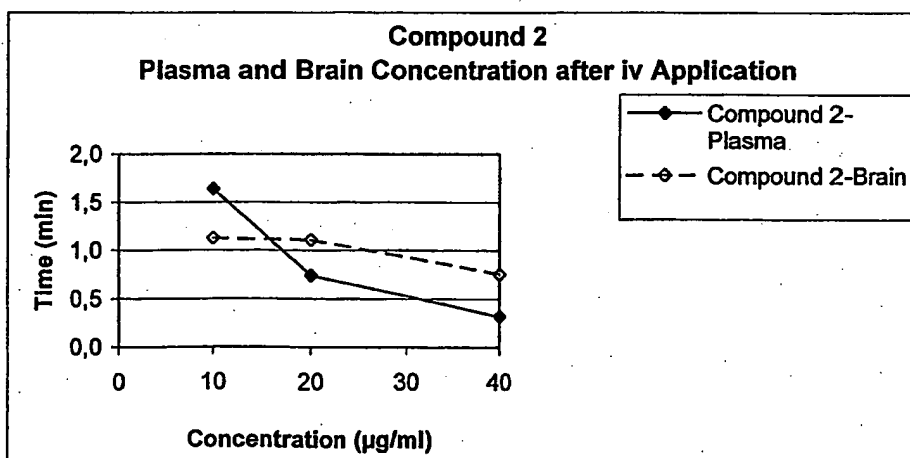
Fig 1:



5

Compound 1: 4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-7-(1-propyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

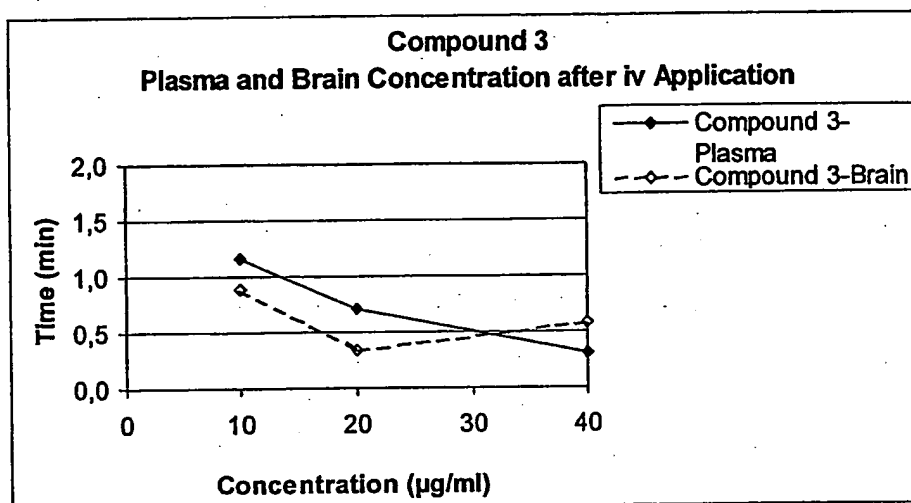
Fig 2:



10

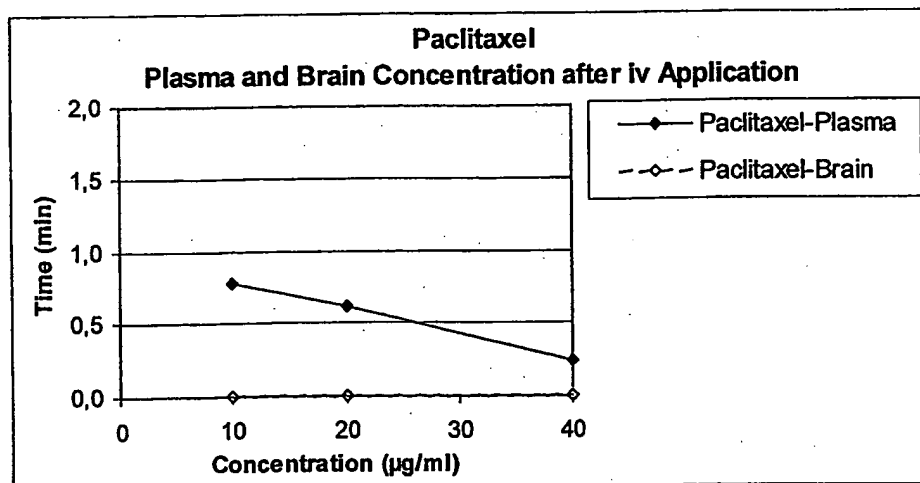
Compound 2: dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

Fig 3:



Compound 3: 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-
5 8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

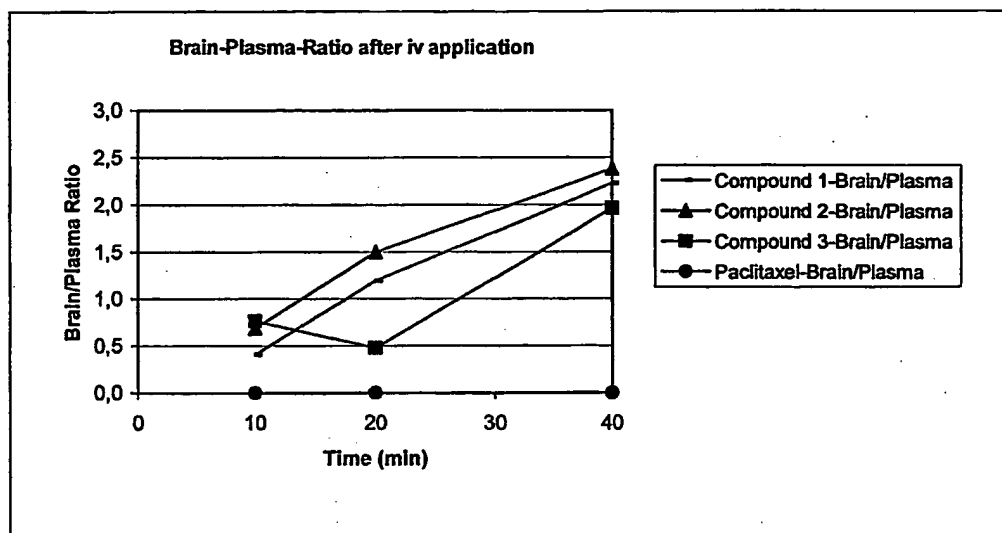
Fig 4:



10

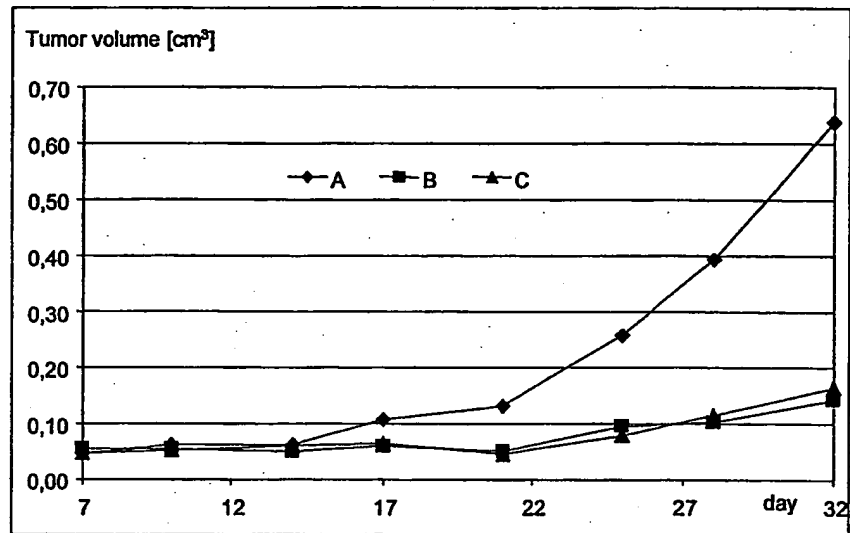
Compound: Paclitaxel

Fig 5:



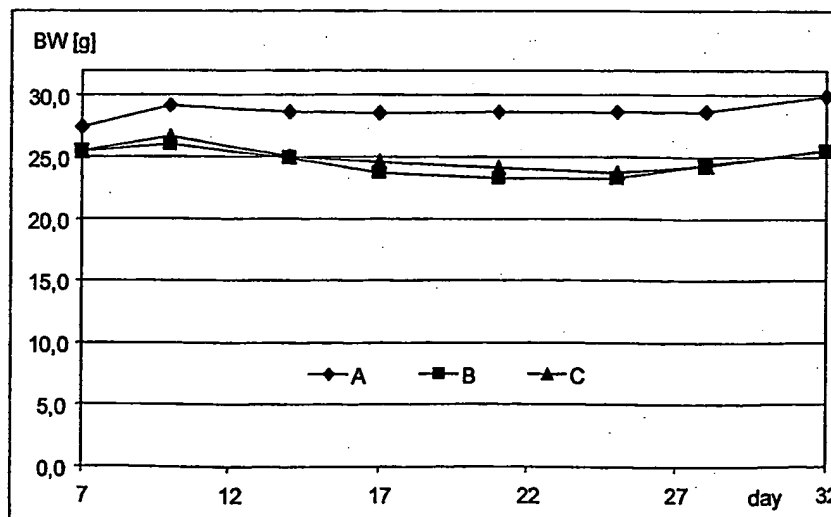
- 5 Compound 1: 4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-7-(1-propyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione;
- Compound 2: dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- Compound 3: 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-
- 10 8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

Fig 16:



5

Figure 7:



10

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/02085

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/428 A61K31/423 A61K31/4709 A61K31/427 A61K31/4427
 A61P25/28 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 92255 A (KOSAN BIOSCIENCES INC ;ASHLEY GARY (US); FARDIS MARIA (US); SANTI) 6 December 2001 (2001-12-06) page 39, line 18-20 page 41, line 7 claims 17,18,21,22	1-7,9, 13,14
Y		1-14
X	WO 99 67253 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); NICOLAOU KYRIACOS) 29 December 1999 (1999-12-29) page 3, paragraph 2 claims 1-8	1-6,9, 13,14
Y		1-14
	-/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

21 May 2003

Date of mailing of the international search report

28/05/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3018

Authorized officer

Bazzanini, R

Internal Application No
PCT/EP 03/02085

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 02514 A (SQUIBB BRISTOL MYERS CO) 21 January 1999 (1999-01-21) cited in the application page 9, line 5,6 page 9, line 21 -page 10, line 9 claims 1,2,4	1-6,9, 13,14
Y	---	1-14
X	WO 99 62510 A (ANGIOTECH PHARM INC ;HUNTER WILLIAM L (CA)) 9 December 1999 (1999-12-09) claims 1,2,6,9,12	1-6,9, 13,14
Y	---	1-14
X	WO 01 24763 A (IMMUNOGEN INC ;CHARI RAVI V J (US)) 12 April 2001 (2001-04-12) claims 1,2,18-20,31,32	1-6,9, 13,14
Y	---	1-14
X	LARNER A.J.: "Neuronal apoptosis as a therapeutic target in neurodegenerative disease." EXPERT OPINION ON THERAPEUTIC PATENTS, (2000) 10/10 (1493-1518)., XP000109764 page 1508, left-hand column, line 2-10 * page 1508, formulae 47, 48 *	1-6,13, 14
Y	---	1-14
Y	WO 00 66589 A (HOFFMANN JENS ;KLAR ULRICH (DE); BUCHMANN BERND (DE); SKUBALLA WER) 9 November 2000 (2000-11-09) cited in the application page 219, line 1-8 claims 1-21 page 246, line 20-22	1-14
Y	---	1-14
Y	WO 99 07692 A (KLAR ULRICH ;SCHERING AG (DE); BUCHMANN BERND (DE); SKUBALLA WERNE) 18 February 1999 (1999-02-18) cited in the application claims 1-8 page 165, line 6-11	1-14
Y	---	1-14
Y	WO 00 49021 A (KLAR ULRICH ;SCHERING AG (DE); BUCHMANN BERND (DE); SKUBALLA WERNE) 24 August 2000 (2000-08-24) cited in the application claims 1-55 page 94, line 13-20	1-14

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C/(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>NICOLAOU K C ET AL: "Chemical Biology of Epothilones" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 37, no. 15, August 1998 (1998-08), pages 2014-2045, XP002131418 ISSN: 0570-0833 page 2037, left-hand column, paragraph 2 -page 2040, right-hand column, paragraph 3 tables 1-6 figure 10</p> <hr/>	1-14

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13 and 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-6,7,9,11 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Moreover, present claims 1-14 relate to a compound defined (inter alia) by reference to the following parameter: "average distribution coefficient between plasma and brain".

The use of this parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameter the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Also, independent of the above reasoning, an attempt is made to define the compound by reference to its pharmacological profile (i.e. pharmacokinetics), rendering the scope of protection of said claims obscure (Art 6 PCT). It is pointed out that a compound cannot be sufficiently characterized by its pharmacokinetics. The use of such a functional definition is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature (e.g. compounds) to which it refers.

Furthermore, it could be understood that all the compounds falling under formulae of claims 4,6-12 possess the claimed "average distribution coefficient between plasma and brain", which seems to be essential for the treatment of the claimed brain diseases.

Consequently, the search concerning the compounds has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds listed in claims 8,10 and 12.

However some of the compounds listed in claim 8 (i.e. all the compounds of the series "dioxabicyclo") don't seem to correspond to the definition of substituent W given in claim 7 (see "(1-methyl-2" moiety before heterocyclic radical of "dioxabicyclo" compounds of claim 8). Therefore for the "dioxabicyclo" compounds the search has been performed taking into account the substituent W as described in claim 7.

Furthermore, present claims 1-4 relate to the treatment of a disease which actually is not well defined. The use of the definition "brain disease associated with proliferative process" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search concerning the therapeutic application of the claimed compounds has been restricted to the diseases listed in claim 5 and those reported in the description from page 8, line 27 to page 9, line 3.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims searched incompletely: 1-14

Claims searched completely: none

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0192255	A	06-12-2001	AU 6658301 A WO 0192255 A2 US 2002045609 A1	11-12-2001 06-12-2001 18-04-2002
WO 9967253	A	29-12-1999	US 6380394 B1 AU 757854 B2 AU 4774899 A AU 4775299 A BR 9911420 A CA 2334342 A1 CN 1306531 T WO 9967252 A2 WO 9967253 A2 EP 1089998 A2 HU 0102711 A2 JP 2002518504 T NO 20006378 A PL 345327 A1 SK 19712000 A3 TR 200003844 T2 US 6531497 B1	30-04-2002 06-03-2003 10-01-2000 10-01-2000 20-03-2001 29-12-1999 01-08-2001 29-12-1999 29-12-1999 11-04-2001 28-12-2001 25-06-2002 21-02-2001 17-12-2001 11-09-2001 20-04-2001 11-03-2003
WO 9902514	A	21-01-1999	AU 731497 B2 AU 7972098 A BG 104068 A BR 9810555 A CN 1270589 T EE 200000013 A EP 1019389 A2 HU 0103111 A2 JP 2002512634 T LT 99153 A ,B LV 12569 A LV 12569 B NO 20000076 A NZ 501198 A PL 338003 A1 SK 181799 A3 TR 200000065 T2 WO 9902514 A2 ZA 9805938 A	29-03-2001 08-02-1999 29-09-2000 15-08-2000 18-10-2000 15-08-2000 19-07-2000 29-04-2002 23-04-2002 25-08-2000 20-11-2000 20-04-2001 07-01-2000 28-09-2001 25-09-2000 06-08-2001 21-11-2000 21-01-1999 10-01-2000
WO 9962510	A	09-12-1999	US 6495579 B1 AU 4025599 A WO 9962510 A2 US 2002183380 A1 US 2002013298 A1	17-12-2002 20-12-1999 09-12-1999 05-12-2002 31-01-2002
WO 0124763	A	12-04-2001	AU 7988500 A CA 2385528 A1 EP 1229934 A2 WO 0124763 A2	10-05-2001 12-04-2001 14-08-2002 12-04-2001
WO 0066589	A	09-11-2000	DE 19921086 A1 DE 10015836 A1 DE 19954228 A1 AU 4310300 A BG 106053 A	02-11-2000 11-10-2001 13-09-2001 17-11-2000 31-05-2002

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/02085

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0066589	A	BR 0010190 A	08-01-2002
		CA 2371226 A1	09-11-2000
		CN 1349534 T	15-05-2002
		CZ 20013885 A3	17-04-2002
		EE 200100568 A	17-02-2003
		EP 1173441 A1	23-01-2002
		HU 0201010 A2	28-08-2002
		WO 0066589 A1	09-11-2000
		JP 2002543203 T	17-12-2002
		NO 20015278 A	21-12-2001
		SK 15512001 A3	09-05-2002
WO 9907692	A 18-02-1999	DE 19735574 A1	11-02-1999
		DE 19735575 A1	11-02-1999
		DE 19735578 A1	11-02-1999
		DE 19748928 A1	29-04-1999
		DE 19749717 A1	06-05-1999
		DE 19751200 A1	20-05-1999
		DE 19813821 A1	23-09-1999
		AU 9340998 A	01-03-1999
		WO 9907692 A2	18-02-1999
		EP 1005465 A2	07-06-2000
		JP 2001512723 T	28-08-2001
		ZA 9810403 A	15-05-2000
WO 0049021	A 24-08-2000	DE 19908765 A1	24-08-2000
		DE 19954230 A1	15-11-2001
		AU 3156700 A	04-09-2000
		BG 105802 A	29-03-2002
		BR 0008331 A	29-01-2002
		CA 2361278 A1	24-08-2000
		CN 1341115 T	20-03-2002
		CZ 20012951 A3	14-11-2001
		EE 200100431 A	16-12-2002
		WO 0049021 A2	24-08-2000
		EP 1150980 A2	07-11-2001
		HU 0105478 A2	29-06-2002
		JP 2002537301 T	05-11-2002
		NO 20014013 A	18-10-2001
		PL 349863 A1	23-09-2002
		SK 11852001 A3	04-04-2002

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